

thermogravimetry (TG), differential scanning calorimetry (DSC) and infrared spectroscopy (IR). The results of the tests are reported in the following table.

TABLE 25

compound	conditions	DSC					
		TG		IR	Max	Extra	Appearance
		<80° C.	<125° C.		(° C.)	(° C.)	
Form K	0 days	0.47	0.15	Ref	143.7	—	slightly orange
Batch 1	RT/75% RH	2.87	0.19	≠Ref	146.6	64.3	slightly orange
	50° C.	0.32	0.14	~Ref	140.6	45.6	orange
	40° C./75% RH	1.48	3.71	—	—	—	brown oil
Form K	0 days	0.16	0.11	Ref	155.8	—	slightly orange
Batch 2	RT/<5% RH	0.00	0.03	~Ref	156.9	—	slightly orange
	RT/56% RH	0.27	0.03	±Ref	154.6	—	slightly orange
	RT/75% RH	1.82	0.07	≠Ref	149.2	67.0	slightly orange
	50° C.	0.12	0.12	~Ref	156.8	—	slightly orange
	40° C./75% RH	3.26	3.08	—	—	—	brown oil

~Ref: identical with reference

±Ref: similar with reference

≠Ref: different with reference

## Example 23

In the chemical stability test program Form K batch 1 was stored for a period of 1 and 4 weeks under different conditions. These conditions were 40° C./75% RH, 50° C., RT/75% RH and 0.3 da ICH light. Form K batch 2 was also stored for a period of 1 and 4 weeks under different conditions. These conditions were 40° C./75% RH, 50° C., RT/<5% RH, RT/56% RH, RT/75% RH and 0.3 da ICH light. The compound was analysed after storage by HPLC and by visual inspection. The HPLC method used in this study was HPLC method 909. The results of the tests are reported in the following table.

TABLE 26

compound	conditions	HPLC Sum of impurities		appearance	
		1 week	4 weeks	1 week	4 weeks
Form K batch 1	Reference	3.57	—	slightly-orange	—
	0.3 da ICH light	2.93	—	slightly-orange	—
	40° C./75% RH	5.36	>90*	slightly-orange	brown oil
	50° C.	3.99	27.53	slightly-orange	orange
	RT/75% RH	—	3.61	—	slightly-orange
Form K Batch 2	Reference	1.50	—	slightly-orange	—
	0.3 da ICH light	1.17	—	slightly-orange	—
	40° C./75% RH	1.75	>85*	slightly-orange	brown oil
	50° C.	1.46	1.25	slightly-orange	slightly-orange
	RT/<5% RH	—	1.58	—	slightly-orange
	RT/56% RH	—	1.45	—	slightly-orange
	RT/75% RH	—	1.46	—	slightly-orange

## Example 24

A randomized, placebo-controlled, double-blind, multiple dose escalation trial was performed to examine the safety, tolerability and pharmacokinetics of Form A after oral administration twice or three times daily, in healthy subjects. Four

dosages of Form A (400 mg b.i.d., 800 mg b.i.d., 800 mg t.i.d., and 1200 mg t.i.d.) were tested in 4 panels of 9 healthy subjects. Within each panel, 6 subjects were treated with

Form A and 3 subjects with placebo for 13 days with a single intake in the morning of day 14. (b.i.d.=twice daily, t.i.d.=three times daily).

Form A was readily absorbed and concentration-time profiles of Form A after repeated dosing were dependent on the dose administered. Steady-state plasma concentrations were reached generally within 3 days, although  $C_{0h}$  (conc. at administration time) and  $AUC_{24h}$  (area under the curve or bioavailability) slightly decreased over time at all dose levels.  $AUC_{24h}$  and  $C_{ss,av}$  (conc. at average steady-state) were dose-proportional (daily dose) at 400 mg b.i.d., 800 mg t.i.d. and 1200 mg t.i.d., but was more than dose-proportional at 800 mg b.i.d.  $C_{max}$  (maximum conc.) was dose-proportional with

respect to dose per intake. Less than 2% of unchanged Form A was excreted in the urine at all dose levels.

The invention claimed is:

1. A hydrate of the compound (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[[[(4-aminophenyl) sulfonyl] (isobutyl)amino]-1-benzyl-2-hydroxypropyl]carbamate in which the ratio of the compound to water is about 1:0.5 to about 1:3.